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REVIEW

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Roles of long noncoding RNAs and small extracellular vesicle-long noncoding RNAs in type 2 diabetes

Wenguang Chang[1] | Man Wang[1] | Yuan Zhang[1] | Fei Yu[1] | Bin Hu[2] | Katarzyna Goljanek-Whysall[3] | Peifeng Li[1]

[1]Institute for Translational Medicine, The Affiliated Hospital, College of Medicine, Qingdao University, Qingdao, China

[2]The Institute of Medical Sciences (IMS), School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Aberdeen, UK

[3]Department of Physiology, Nursing and Health Sciences, College of Medicine, National University of Ireland, Galway, Ireland

Correspondence
Wenguang Chang and Peifeng Li, Institute for Translational Medicine, The Affiliated Hospital, College of Medicine, Qingdao University, Qingdao, China.
Email: changsubmit@126.com and peifli@hotmail.com

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Abstract

The prevalence of a high-energy diet and a sedentary lifestyle has increased the incidence of type 2 diabetes (T2D). T2D is a chronic disease characterized by high blood glucose levels and insulin resistance in peripheral tissues. The pathological mechanism of this disease is not fully clear. Accumulated evidence has shown that noncoding RNAs have an essential regulatory role in the progression of diabetes and its complications. The roles of small noncoding RNAs, such as miRNAs, in T2D, have been extensively investigated, while the function of long noncoding RNAs (lncRNAs) in T2D has been unstudied. It has been reported that lncRNAs in T2D play roles in the regulation of pancreatic function, peripheral glucose homeostasis and vascular inflammation. In addition, lncRNAs carried by small extracellular vesicles (sEV) were shown to mediate communication between organs and participate in diabetes progression. Some sEV lncRNAs derived from stem cells are being developed as potential therapeutic agents for diabetic complications. In this review, we summarize the current knowledge relating to lncRNA biogenesis, the mechanisms of lncRNA sorting into sEV and the regulatory roles of lncRNAs and sEV lncRNAs in diabetes. Knowledge of lncRNAs and sEV lncRNAs in diabetes will aid in the development of new therapeutic drugs for T2D in the future.

KEYWORDS
diabetes, exosomes, long noncoding RNA, small extracellular vesicle, sorting mechanism

1 | INTRODUCTION

The incidence of type 2 diabetes (T2D) is rapidly increasing with the prevalence of obesity and sedentary lifestyles. Prevention of diabetic complications is the main goal of diabetic treatment,[1] but the current treatment cannot achieve satisfactory effects; for example, half of patients with T2D present with microvascular complications, and 27% present with macrovascular complications in an observational study of 28 countries in Asia, Africa, South America and Europe.[2] Even on the basis of cohort studies from developed countries, the relative risk of complications among patients with diabetes was estimated to be higher than in people without diabetes.[3] Thus, it is important to clarify the pathological mechanism of T2D to carry out more effective therapeutic strategies.

Noncoding RNAs control various levels of gene expression, including chromatin architecture/epigenetic memory, transcription, RNA splicing, editing, translation and turnover.[4] Accumulated evidence has shown that noncoding RNAs have an essential regulatory role in the progression of diabetes and its complications. The roles of small noncoding RNAs, such as miRNAs, in T2D have been extensively investigated, while the function of long noncoding RNAs (lncRNAs) in T2D has been unstudied. Many lncRNAs, such as HOTAIR, MEG3, LET, MALAT1, MIAT, CDKN2BAS1/ANRIL, XIST and GAS5, were shown to change in type 2 diabetic conditions.[5] In addition, lncRNAs carried by small extracellular vesicles (sEV), such as H19, MALAT1, HOTAIR and SNHGs, were shown to mediate communication between organs and participate in diabetes progression. In this review, we summarize the current knowledge relating to lncRNA biogenesis, the mechanisms of lncRNA sorting into sEV, and the regulatory roles of lncRNAs and sEV lncRNAs with a focus on T2D. We hope to aid further therapeutic drug development for T2D.

2 | BIOGENESIS AND CHARACTERIZATION OF LONG NONCODING RNAs

Long noncoding RNAs (lncRNAs) are RNA transcripts more than 200 nucleotides (nt) in length that do not encode proteins. LncRNAs are often classified by their gene location relative to nearby protein-coding genes.[6] As shown in Figure 1A, lncRNA transcripts localized between exons of a protein-coding gene are defined as intronic lncRNAs. LncRNAs overlapping exons but transcribed in the opposite direction are defined as antisense lncRNAs. Long intervening noncoding RNA (lincRNA, also called long "intergenic" noncoding RNA) refers to lncRNA generated from intergenic genes that do not overlap with exons of either protein-coding or other non-lincRNA genes.[7] The biogenesis of lncRNAs is similar to that of mRNAs; for example, both are spliced and modified with 5′-end m^7G caps and 3′-end poly(A) tails. However, lncRNAs have some unique features that can distinguish them from mRNAs, such as the presence of fewer and longer exons than mRNAs, relatively low expression, the ability to generate circular RNAs or pre-miRNAs, and strict localization.[8] LncRNAs are transcribed mainly by Pol II, and their expression is highly regulated. SWI/SNF promotes and CAF-1 inhibits transcriptional initiation and direction, while Dicer and MYC participate in the regulation of elongation[9] (Figure 1A). In the chromatin state, some antisense lncRNA genes are repressed by chromatin remodeling complexes (Swr1, Isw2, Rsc and Ino80), therefore inhibiting the corresponding mRNA expression.[10] It is known that the transcription and splicing efficiency of lncRNAs are low, which causes them to primarily accumulate in the nucleus and form nuclear speckles[11] (Figure 1B), which act as a hub to coordinate all of the nuclear gene expression regulation steps.[12] To date, lncRNAs have been proven to participate in molecular and genomic modulation in various ways,[13] including (1) bringing two distant genes closer (scaffolds, Figure 1C-I); (2) binding to transcription

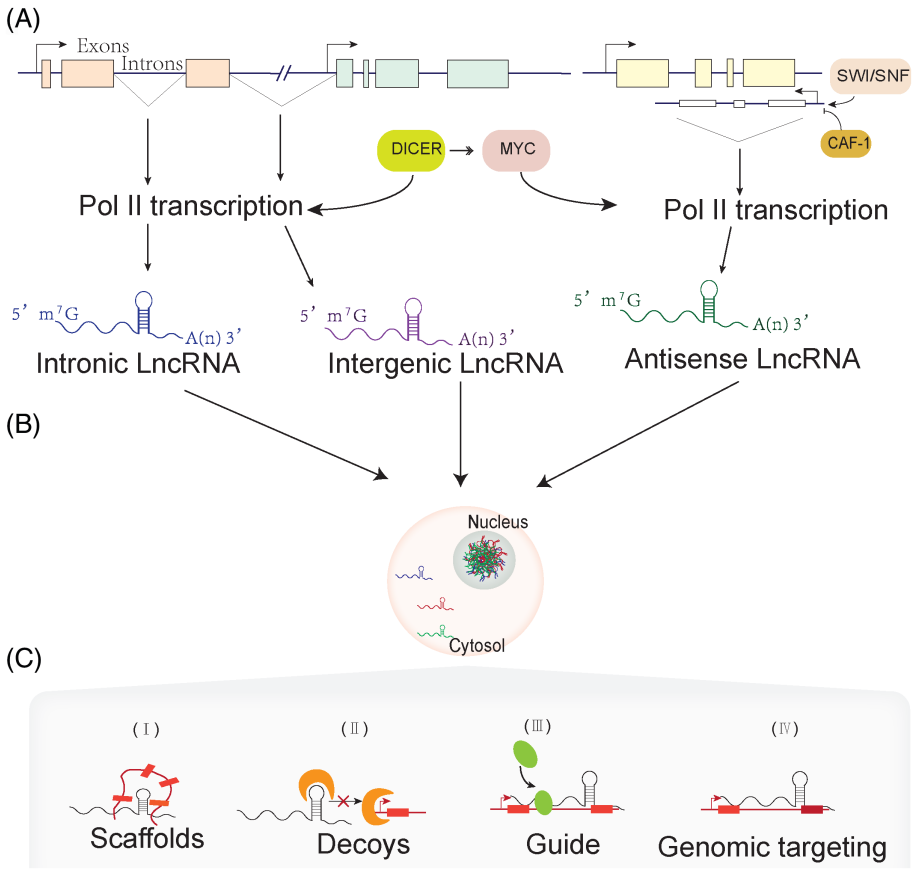

FIGURE 1 LncRNA biogenesis and functions. (A) lncRNAs classified according to locations of transcripts. Intronic lncRNAs are generated from introns inside a coding-protein gene. Antisense lncRNAs are transcripts from the opposite direction of a protein-coding gene. LincRNAs are generated from intergenic genes. (B) The majority of lncRNAs are transcribed by Pol II, which is regulated by MYC and DICER, and lncRNAs are prone to accumulation in the nucleus. (C) LncRNAs function as scaffolds, decoys, genomic targets and guide regulatory proteins

factors to inhibit gene transcription (decoys, Figure 1C-II); (3) guiding regulatory proteins to gene sequences, thus affecting gene expression (Figure 1C-III); and (4) directly binding to gene sequences to affect gene expression (genomic targeting) (Figure 1C-IV). In pancreatic and diabetic conditions, for example, Hi-LINC25 binds to transcription factors in islets; H19, LncSHGL and MIST bind to proteins or RNA-binding proteins (RBPs) to regulate glucose metabolism-related gene expression; and most of the studied lncRNAs, such as DRAIR, H19 and MALAT1, were shown to target miRNAs to regulate their target gene expression.

3 | ROLES OF lncRNAs IN DIABETES

Although the functional roles of lncRNAs in T2D have only been revealed in recent years, accumulated evidence has demonstrated the biological or pathological roles of lncRNAs in the progression of diabetes and its complications. The mechanisms of lncRNA function in this disease involve pancreatic β cell homeostasis modification, lipid metabolic regulation and inflammatory responses[14–16] (Table 1).

3.1 | LncRNAs and β cell homeostasis

Pancreatic β cell dysfunction is a common pathological factor in both type 1 diabetes and T2D. Studies have shown that lncRNAs regulate islet function in various ways. For example, the depletion of lncRNA-HI-LNC25, a lncRNA specifically expressed in islet cells, downregulates the expression of the islet transcription factor GLIS3, a mutation that leads to diabetes.[17] This finding indicates a role of lncRNAs in islet development. In addition, the expression of islet lncRNA-HI-LNC78 and lncRNA-HI-LNC80 is repressed in pancreatic progenitors but is activated in adult islets. Moreover, their expression is also increased in response to high glucose (HG) stimulation,[17] showing the potential regulatory function of lncRNAs in glucose homeostasis. In addition, knockout of β cell lncRNA-βlinc1 results in defective islet development and disruption of glucose homeostasis in adult mice.[18] LncRNA-H19 expression promoted the proliferation of β-cells by targeting the let-7/AKT pathway in adult mice.[19] All these results demonstrate the essential roles of lncRNAs in the regulation of pancreatic development.

3.2 | LncRNAs and adipose development

White adipose tissue (WAT) and brown adipose tissue (BAT) were reported to regulate lipid metabolism and thermogenesis, respectively.[43] Brown and beige adipocytes are known to protect humans and mice from obesity and diabetes, and some adipose-specific lncRNAs have been shown to affect adipocyte metabolism by regulating mitochondrial function. For example, BATE1 and Blnc1 promote brown and beige adipocyte differentiation and function.[20] Blnc1 protects against diet-induced obesity by promoting mitochondrial biogenesis in WAT, which accelerates glucose metabolism.[21] LINC00473, a lncRNA specifically expressed in human BAT adipocytes, is decreased in obesity and T2D. LINC00473 was shown to colocalize with mitochondrial and lipid droplet proteins in the cytosol and regulate lipolysis, respiration and transcription of genes associated with mitochondrial oxidative metabolism, thus modifying adipocyte function.[22] In addition, lncRNA-Adi is highly expressed in adipose tissue-derived stromal cells (ADSCs) and enhances adipogenesis by interacting with miR-499,[23] which is a microRNA that has been shown to participate in the regulation of mitochondrial function.[44] Moreover, epigenetic modification of certain lncRNAs affects adipose development. A recent report showed that maternal obesity increases DNA methylation of an antisense lncRNA-Dio3os promoter in oocytes and offspring brown fat. This is because methylation inhibits Dio3 expression, and as a result, BAT development is inhibited by reduced thyroid hormone synthesis.[24] Interestingly, this maternal repression can be passed to offspring, suggesting that the regulation of lncRNA function in adipose tissue could be transmitted to subsequent generations.

3.3 | LncRNAs and glucose homeostasis

Liver gluconeogenesis is the main target for glucose homeostasis regulation. An RNA sequencing analysis in the liver of diabetic mice showed that lncRNA-H19 depletion increases FOXO1 translocation to the nucleus, which is an essential transcriptional regulator for gluconeogenesis gene expression.[25] LncRNA-antisense betaine-homocysteine methyltransferase-antisense (Bhmt-AS) is overexpressed in the liver of diabetic mice in response to gluconeogenic hormonal stimuli, and it specifically regulates Bhmt expression and hepatic gluconeogenesis,[26] suggesting that lncRNAs have a role in the regulation of liver gluconeogenesis. Concurrently, lncSHGL enhances the translation efficiency of CALM mRNAs by recruiting hnRNPA1 in the liver of obese mice, which activates the PI3K/AKT pathway in the absence of insulin,[27] revealing an alternative glucose consumption pathway regulated by lncRNAs. In addition, metformin, a first-line drug for diabetic treatment and an AMPK activator, reduces the glucose effect by accelerating glycolysis and inhibiting gluconeogenesis. Metformin induces different expression levels of lncRNAs. Studies have shown that 456 lncRNAs are upregulated and 409 lncRNAs are downregulated by cAMP stimuli, and nearly half of them are attenuated by metformin treatment.[45] Another study also showed a similar result, in which metformin and resveratrol treatment altered lncRNA profiles in the livers of obese mice, and those lncRNAs regulate insulin signaling pathways.[46] Thus, metformin treatment may exert its anti-diabetic effect by altering lncRNA expression.

In skeletal muscle, lncRNAs have a pivotal role in muscle biogenesis and insulin response The skeletal muscle-specific lncRNAs lincYY1,[47] Dum,[48] and Linc-RAM[49] were shown to regulate myogenic differentiation and biogenesis. LncRNA profile analysis of insulin-resistant C2C12 cells treated with palmitic acid showed 70 upregulated and 74 downregulated lncRNAs, which were associated with fatty acid oxidation, lipid oxidation, the PPAR signaling pathway and

TABLE 1 LncRNAs and their effects in T2D

LncRNA	LncRNA origin	Experimental species	Possible molecular mechanisms	Ref.
β cell related				
HI-LNC25/HI-LNC78/HI-LNC80	Pancreatic islet tissue	Human	Target islet transcription factor GLIS3	17
β-linc 1	Pancreatic islet tissue	Human	Affect endocrine cell differentiation	18
H19	Pancreatic islet tissue	T2D mice/Rat β cells	Promote β cell proliferation via let-7/AKT	19
Adipose development related				
BATE1/Blnc1	BAT	Mice	Promote brown and beige adipocyte differentiation	20
Blnc1	BAT	Mice	Promote mitochondrial biogenesis	21
LINC00473	BAT progenitor cells	Human	Regulate mitochondrial oxidative metabolism	22
Adi	ADSCs	Rats	Promote adipogenesis via targeting miR-499	23
Dio3os	Fetal BAT from maternal obesity	Mice	Inhibit brown adipose development via maternally imprinted	24
Glucose homeostasis related				
H19	Livers of db/db mice	Mice	Inhibit gluconeogenesis via Foxo1	25
Bhmt-AS	Livers of db/db mice	Mice	Promote gluconeogenesis	26
lncSHGL	Livers	Mice	Inhibit gluconeogenesis via interacting with hnRNPA1	27
Different expressed-144 lncRNAs	C2C12 skeletal muscle cells	FFA induced insulin resistant cells	Associated with FAO metabolism and insulin signaling	28
Different expressed-401 lncRNAs	Skeletal muscles	Rats	Associated with mRNA that regulate glucose metabolism	29
H19	Skeletal muscles	Rats	Promote glucose metabolism via DUSP27/AMPK	30
H19	Primary satellite cells isolated from muscles	Mice	Promote FAO gene expressions via interacting with hnRNPA1	31
Inflammatory related				
LYPLAL1-DT	Leukocytes	Human umbilical vein endothelial cells	Inhibit inflammation via miR-204-5p/SIRT1	32
Linc-Gm4419	Renal tissue/Mesangial cells	Mice/HG treated cells	Promote inflammation via NLRP3	33
MALAT1	Brain tissue	Human T2D with OSA	Promote inflammation via miR-224-5p/NLRP3	34
MALAT1	Peripheral blood mononuclear cells	NA	Promote inflammation via miR-1-3p	35
SNHG5	Serum/HK2 cells	Human/HG treated HK2 cells	Promote inflammation via miR-224-5p	36
H19	Retinal epithelial cells	HG treated retinal epithelial cells	Inhibit inflammation via miR-93/XBP1	37
Lnc uc.48	Serum/Macrophages	Human/HG and FFA treated cells	Promote inflammation via $P2X_7R$/ERK	38
Dnm3Os	BMDM	Mice	Promote inflammatory gene expressions via global histone modifications	39
DRAIR	Monocytes	Human	Inhibit inflammation via epigenetic mechanisms	40
MIST	Adipose macrophages	Mice	Inhibit inflammation via interacting with PARP-1	41
Tcons_00077866	Pancreatic β-TC6 cells	Mice	Promote inflammation via miR-297b-5p/SAA3	42

Abbreviations: ADSCs, adipose derived stromal cells; BAT, brown adipose tissue; BMDM, bone marrow derived macrophages; FFA, fatty acid; HG, high glucose; OSA, obstructive sleep apnea; T2D, type 2 diabetes.

the insulin signaling pathway.[28] Meanwhile, dysfunction of lncRNA and its highly associated mRNA or prediction of target mRNA (NONRATG017315.2-Pdk4, NONRATG003318.2-Stc2, NONRATG011882.2-Il15, NONRATG013497.2-Fbxw7, MSTRG.1662-Ucp3) affects hyperglycemia, glucose intolerance, and increased fatty acid oxidation in diabetic Goto-Kakizaki rats.[29] In addition, AMPK is an energy sensor that regulates glucose and fatty acid metabolism. LncRNA-H19 regulates AMPK activation by promoting atypical dual-specificity phosphatase (DUSP27).[30] Another report showed that H19 interacts with hnRNPA1, thereby increasing fatty acid oxidation-related transcriptional genes in skeletal muscle cells.[31] These results suggest that lncRNAs have an important role in regulating glucose and fatty acid metabolism in skeletal muscles.

3.4 | LncRNAs and inflammatory responses

Inflammation participates in the progression of T2D.[50] Vascular dysfunctions induced by excessive inflammation are major pathological factors that cause diabetic retinopathy, nephropathy and neuropathy.[51] Inflammatory tissue, including adipose tissue, the liver, pancreatic islets, the vasculature and circulating leukocytes, release cytokines, such as TNFα, IL-6 and IL-1β. They act in an autocrine and paracrine manner to promote vascular dysfunction by activating the c-JUN N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) pathways. However, the initiation of the inflammatory process remains unclear. On the one hand, a large cytoplasmic multiprotein complex called the inflammasome, especially the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, was shown to control the activation of IL-1β in the progression from obesity to T2D by recognizing microbial products.[52] On the other hand, free fatty acids activate Toll-like receptor 4 (TLR-4) in adipocytes, and macrophages also lead to the upregulation of NF-κB, TNFα and IL-6.[53] LncRNAs have been found to participate in the inflammatory response in T2D. LncRNA profiles of leukocytes from T2D patients with macrovascular diseases showed that LYPLAL1-DT has protective effects on endothelial cells under HG and inflammatory conditions.[32] The expression of lncRNA ANRIL was upregulated in T2D patients and in HG-induced podocytes. LncRNA ANRIL silencing attenuated HG-induced NLRP3 inflammasome activation and cytokine release.[54] A similar result was observed for lncRNA-GM4419 in renal tissue from T2D nephropathy mice and HG-induced mesangial cells.[33] In addition, MALAT1[34,35] and SNHG5[36] were shown to regulate inflammation by targeting NLRP3 in T2D brain tissue or neuron cells, and SNHG2[55,56] was reported to modulate inflammation by regulating NF-κB, while H19[37] and lnc uc.48[38] regulate inflammation by activating endoplasmic reticulum stress proteins (XBP1 or ERK), indicating that inflammatory responses are differentially regulated by lncRNAs. In addition, some lncRNAs regulate inflammation by epigenetic modification of inflammation-related genes. For example, type 2 diabetic conditions induce lncRNA Dnm3os expression via NF-κB activation, and Dnm3os localizes to the nucleus and alters global histone modifications, thus upregulating inflammation in macrophages.[39] LncRNA DRAIR was downregulated in T2D, and overexpression DRAIR increased anti-inflammatory but inhibited proinflammatory genes via epigenetic mechanisms.[40] Moreover, lncRNAs participate in the regulation of inflammation in several organs. Except for the renal tissue, brain tissue and retinal tissue mentioned above, macrophage inflammation-suppressing transcript (Mist) was decreased in adipose tissue macrophages from high-fat diet-fed mice. Mist interacts with poly ADP-ribose polymerase-1 (PARP1), an activator of inflammatory gene expression and interruption of the Mist-PARP1 interaction by obesity promotes inflammatory responses.[41] Knockdown of lncRNA TCONS_00077866 (lnc866) inhibited the stearic acid-induced reduction in insulin secretion and β-cell inflammation.[42] Therefore, inflammation regulation by lncRNAs has an important role in the incidence and progression of diabetes and makes them possible targets for diabetes therapy.

Based on the functional roles of lncRNAs in diabetes, some lncRNAs have been developed as diagnostic and therapeutic agents for diabetes and its complications. In the clinic, lncRNA ENST00000550337.1 from peripheral blood has high diagnostic value for prediabetes and T2D.[57] LincRNA RP1-90L14.1 was shown to be related to the pathology of diabetic retinopathy.[58] In addition, two other clinical trials are ongoing (NCT04638556 and NCT04767750). Moreover, researchers found that some lncRNAs are wrapped in extracellular vesicles (EV), which carry them into various organs and function as mediators for cell–cell communications.

4 | EV BIOGENESIS AND lncRNA SORTING MECHANISMS

EV are double-membrane vesicles that are released into extracellular spaces by various types of cells. They cannot replicate and do not have a functional nucleus. EV subtypes are defined by size as large EV (200–2000 nm) or small EVs (sEV, 50–200 nm), by chemical composition as $CD63^+$/$CD81^+$ or Annexin A5 stained, or by the biogenesis pathway as endosomal derived EV (also called exosomes) or plasma membrane derived EV (also called microparticles or microvesicles). sEV are nomenclature by size; they are produced either by direct budding from the plasma membrane or by the fusion of multivesicular bodies (MVBs) with the plasma membrane[59] (Figure 2A). MVBs are generated via a two-step endocytosis process: an intraluminal vesicle (ILV) is first formed by late endosome invagination, and then ILVs modify the cargos to generate MVBs. Commonly used markers of sEV, such as CD9 and CD63, are vital proteins that participate in endosome-derived sEV biogenesis.[60] Thus, the widely used term "exosomes" refers explicitly to sEV that are generated via the endosome pathway. However, because of the limitations of purification methods, it is impossible to separate the vesicles based on their biogenesis pathways. According to MISEV 2018,[61] researchers are recommended to categorize EV by size since most studies have not verified the vesicle biogenesis pathway. In this

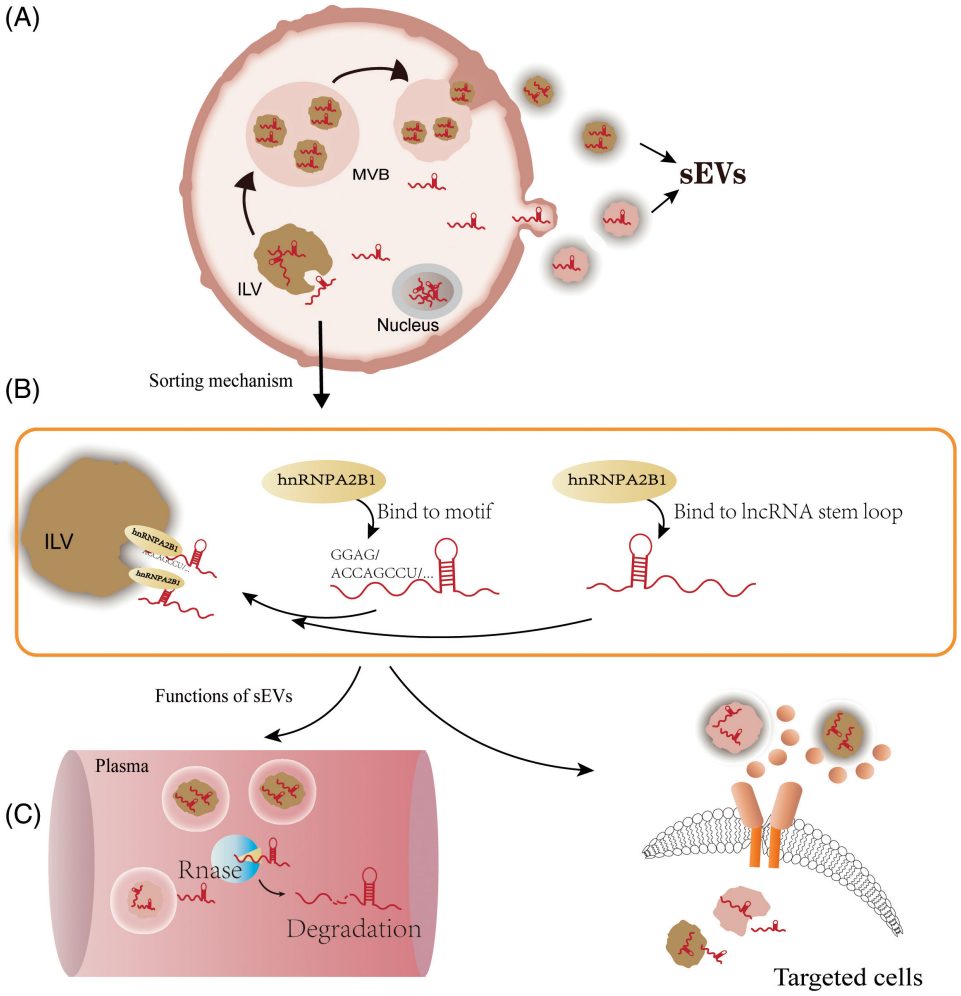

FIGURE 2 Biogenesis of small extracellular vesicle (sEV) and mechanisms of lncRNA sorting into EVs. (A) sEV generated from multivesicular body fusion with the plasma membrane or direct budding from the plasma membrane; (B) HnRNPA2B1 was shown to guide lncRNA sorting into sEVs by directly binding to stemloops or binding specific sequence motifs. (C) LncRNAs packaging into EV are important to exert their optimal functions. Left, EV protect lncRNAs from degradation by RNase; Right, EV help lncRNAs recognize targeted cells

paper, sEV refer to EV less than 150 nm, regardless of the biogenesis pathway. The generation of EV was thought to be a method of quality control to eliminate the "bad" or "useless" proteins.[62] In recent years, many studies have shown that these vesicles carry bioactive cargoes, including lipids, proteins, and nucleic acids, which mediate cell–cell communication and regulate biological functions in recipient cells.[63,64]

Recent studies have shown that noncoding RNAs are sorted into EVs, but the molecular mechanism is still unclear. Several proteins or lipids involved in this process have been identified. For example, RBPs, such as heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1), are revealed to guide the sorting of miRNA into EV by interacting with the GGAG motif at the 3′-end of the miRNAs.[65] The binding specificity of hnRNPA2B1 with the GGAG motif was confirmed by RNA pull-down analysis, which showed that this interaction was seriously impaired by mutations in the "GGAG" sequence. Overexpression or knockdown of hnRNPA2B1 promotes or suppresses lncRNA-H19 sorting into sEV in non-small cell lung cancer (NSCLC) cell lines.[66] In addition, hnRNPA2B1 may also function in the sorting of lncRNAs into sEV. This was evidenced by knockdown or overexpression of hnRNPA2B1, which downregulates or enhances the levels of lncRNA-AFAP-AS1 and lncRNA-AGAP-AS1 in sEV.[67,68] This suggests that the sorting of lncRNAs and miRNAs might share a similar pathway. On the other hand, KRAS mutation, a gene mutation promoting colorectal cancer spread, was shown to affect miRNA sorting into EV in colorectal cancer cells[69]; however, this mutation has no detectable effect on lncRNA sorting, suggesting that the sorting mechanisms of lncRNAs are at least partially distinct from those of miRNAs.[70] Consistently, a study of the role of sEV lncRNA-LNMAT2 in lymphatic metastasis of bladder cancer showed that hnRNPA2B1 binds to LNMAT2 via a stem–loop structure located in the 1930–1960 nt region.[71] Coincidentally, a bioinformatic analysis of mRNAs sorted into sEV identified three motifs, ACCAGCCU, CAGUGAGC and UAAUCCCA, which may function as cis-acting elements guiding RNAs (more than 20% were lncRNAs) to sEV. Strikingly, those motifs from different RNAs were predicted to form similar secondary structures,[72] suggesting that motif specificity and the secondary structures are critical for lncRNA sorting into EV (Figure 2B).

LncRNAs packaging into EV are important to exert their optimal functions (Figure 2C). The double membrane of EV protects them from degradation by cellular RNase, making them have longer than average half-lives.[73] Proteins or lipids expressed on sEV membranes facilitate their ability to transfer from donor to recipient cells to trigger phenotypic changes in acceptor cells.[64] In particular, some

lncRNAs were shown to be abnormally expressed in sEV under disease conditions, showing their considerable promise as novel biomarkers of disease.

5 | ROLES OF sEV lncRNAs IN DIABETES

5.1 | sEV lncRNA profiling

Profiles of sEV lncRNAs in various diseases have been described.[74–76] Compared with their expression in healthy controls, plasma sEV lncRNAs were found to be expressed differently under distinctive diabetic conditions. For example, lncRNAs are aberrantly expressed in umbilical cord blood sEV from patients with gestational diabetes mellitus.[77] HG-treated tubular epithelial cell-derived sEV carried 93 upregulated lncRNAs and 76 downregulated lncRNAs.[78] Similarly, 21 lncRNAs, including SNHG5 and C430049B03Rik, were found to be differentially expressed under high-glucose conditions in three kinds of progenitor cell lines.[79] In response to proinflammatory cytokine stimuli, human islet cell-derived sEV contained 31 lncRNAs whose levels were altered.[80] In addition, some lncRNAs were enriched specifically in sEV, and lncRNA-p3134 levels were found to be four times higher in serum sEV than in controls but remained nearly unchanged in sEV-free serum. Further experimental results showed that lncRNA-p3134-containing sEV promote glucose-stimulated insulin secretion in β cells, thus regulating pancreatic functions,[81] indicating that the sorting mechanisms of lncRNAs have an important role in lncRNA-mediated pancreatic function regulation. To date, several sEV lncRNAs have been found to participate in the progression of diabetes and diabetes-related diseases.[82] Some of them are being developed as promising therapeutic agents for diabetic complications (Table 2).

5.2 | H19

LncRNA-H19 is a highly conserved maternally encoded gene. H19 has been shown to be associated with embryonic growth control, tumor growth and T2D.[96] Several clinical studies revealed that serum H19 levels in T2D patients were lower than those in healthy controls.[85,97] Patients with diabetes often suffer from slow wound repair and exhibit diabetic foot ulcers. H19 promotes wound healing in diabetic conditions.[98] Experimental evidence showed that sEV H19 derived from adipose mesenchymal stem cells (ADSCs) accelerates wound healing in diabetic mice, and silencing H19 in ADSCs decreased H19 accumulation in sEV, which inhibited skin fibroblast proliferation, migration and invasion by targeting miR-19b/SOX9.[83] Overexpression of H19 in MSC-derived sEV promotes wound healing in diabetic foot ulcers by sponging miRNA-152-3p, thereafter upregulating phosphatase and tensin homolog (PTEN), a regulator of cell proliferation and growth[84] (Table 2). Furthermore, sEV-mimicking nanovesicles engineered to increase H19 levels were proven to be an effective nanodrug delivery system. These nanovesicles had a strong ability to rescue cell proliferation signals that were impaired by HG in a diabetic rat model.[86] In addition, H19 carried in sEV was reported to be associated with obesity-induced retardation of fracture healing. Utilizing normal MSC-derived sEV can reverse abnormal fracture healing via the miR-467/HoxA10 axis[85] (Table 2).

5.3 | MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a long noncoding RNA with a single exon that is predominantly found in nuclear speckles, and it is evolutionarily conserved among mammalian species.[99] MALAT1 was first found to be associated with

TABLE 2 sEV-LncRNAs and their effects in T2D

sEV-LncRNA	sEV-origin	Target cells	Functions/molecular mechanisms	Ref.
p3134	Human serum	β-cells	Promote glucose stimulated insulin secretion	81
H19	Mice ADSC	Skin fibroblasts	Promote wound healing via miR-19b/sox9	83
H19	Mice BMMSC	Skin fibroblasts	Promote wound healing via miR-152-3p/PTEN	84
H19	Mice BMMSC	Osteoblasts	Promote fracture healing via miR-467/HoxA10	85
H19	Manual nanovesicles	Dermal microvascular endothelial cells	Promote cell proliferation	86
MALAT1	Human ADSC	Hippocampal cells	Increase neuro survival via SRSF2/PKCδII	87
MALAT1	Mice adipocytes	Hypothalamic neurons	Increase appetite and weight	88
MALAT1	Human ADSC	Skin fibroblasts	Accelerate wound healing via miR-124/wnt/β-catenin	89
MALAT1	HUVEC	Dendritic cells	Prevent atherosclerosis by inhibiting ROS	90
HOTAIR	Mice Adipose tissue	Intestinal cells	Promote intestinal cell proliferation via NF-κB	91
HOTAIR	Mice BMMSC	HUVEC	Promote wound healing via upregulate angiogenic proteins	92
SNHG2	Human Macrophages	HUVEC	Inhibit apoptosis of endothelial cells	93
SNHG7	Human BMMSC	Human retinal endothelial cells	Repress HG induced endothelial dysfunction	94
SNHG9	Human adipocytes	HUVEC	Alleviated inflammation	95

Abbreviations: ADSC, adipose derived stem cells; BMMSC, bone marrow mesenchymal stem cells; HG, high glucose; HUVEC, human umbilical vein endothelial cells; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; Sox9, SRY-Box Transcription Factor 9; SRSF2, Serine and Arginine Rich Splicing Factor 2.

metastasis in NSCLC patients.[100] Its overexpression increases the risk of metastasis in various cancers.[101] MALAT1 levels were reported to increase in vascular endothelial cells and retinal endothelial cells exposed to HG treatment,[102,103] as well as in macrophage-derived sEV by exposed to HG treatment.[104] However, serum MALAT1 levels were reported to decrease in patients with T2D, as well as sEV MALAT1 levels in the serum of T2D patients.[105] The functional role of sEV MALAT1 in obesity and diabetes-related diseases varies across tissues and organs. A lncRNA analysis of sEV derived from human ADSCs showed that omental depots of obese donors had increased MALAT1 levels compared with those of omental depots of lean donors.[106] A study also showed that adipocytes of obese mice secreted MALAT1-containing sEV, which were transferred to hypothalamic anorexigenic neurons by injection into lean mice and increased appetite and weight in lean mice.[88] This result is consistent with a previous study, which showed that human ADSC-derived sEV containing MALAT1 increase neuronal survival by mediating PKCδII splicing via SRSF2 in the hippocampal cell line (Table 2). Interestingly, it was found that insulin treatment dramatically increased the association of MALAT1 and splicing factors,[87] suggesting that obesity and insulin could affect the crosstalk between organs via MALAT1 in sEV. However, although a high level of MALAT1 could increase the risk of tumorigenesis, ADSC-derived sEV containing MALAT1 were shown to accelerate wound healing by targeting the miR-124/Wnt/β-catenin pathway (Table 2), and ADSC-sEV subjected to MALAT1 knockdown impaired their ability to protect skin fibroblast proliferation against H_2O_2 treatment.[89] In addition, human vascular endothelial cell (HUVEC)-derived sEV exhibited lower MALAT1 expression after oxidized low-density lipoprotein (ox-LDL) treatment. MALAT1-highly enriched sEV from ox-LDL-treated HUVECs inhibited ROS accumulation and dendritic cell maturation by interacting with and activating NFR2 (Table 2), thus preventing atherosclerosis development.[90]

5.4 | HOTAIR

HOX antisense intergenic RNA (HOTAIR) is a 2.2 kb, spliced and polyadenylated transcript that is repressed in the antisense direction at the HOXC locus on chromosome 12 in humans. HOTAIR is highly conserved among species and was the first lncRNA reported to function in trans.[107] Studies have shown that the serum levels of HOTAIR in patients with T2D, diabetic retinopathy and diabetic cardiomyopathy are significantly increased.[108–110] This elevation is also found in different tissues in diabetic states, such as liver tissues,[111] kidney tissues[112] and myocardial tissues.[110] Interestingly, HOTAIR is expressed only in gluteal but not abdominal adipose tissue, and transfecting HOTAIR into abdominal preadipocytes promotes their differentiation into adipocytes.[113] Further study showed that obese subjects with sedentary lifestyles have higher sEV HOTAIR expression in the serum. An experiment showed that gluteal-femoral fat increases the secretion of sEV HOTAIR, which is taken up by intestinal cells and promotes intestinal cell stemness/proliferation by binding to activated NF-κB[91] (Table 2), indicating the regulatory role of HOTAIR in metabolic homeostasis. In addition, engineered sEV isolated from HOTAIR-overexpressing MSCs promoted angiogenesis and wound healing in a diabetic mouse model. Furthermore, MSC-derived sEV carrying HOTAIR upregulate angiogenic protein expression in endothelial cells.[92]

5.5 | SNHGs

Small nucleolar RNAs (snoRNAs) are a group of small noncoding RNAs that are localized in the nucleus. snoRNAs are generated from introns; if a full-length transcript includes introns and exons from a snoRNA gene, it will function as a lan lncRNA, named a small nucleolar RNA host gene (SNHG).[114,115] The SNHG family contains various members, from SNHG1 to SNHG13, SNHG15, SNHG17, SNHG20 and SNHG28.[116] Some of these members were recognized as aggressive tumor promoters. For example, SNHG2 was shown to be enriched in sEV compared with their parent cells and to function as an apoptosis marker in tumor cell lines.[117] SNHGs were also shown to be adipogenesis regulators. Overexpression of SNHG2 (also known as GAS5) was shown to reduce lipid accumulation in 3T3-L1 adipocytes,[118] and SNHG2 was found to be negatively correlated with MSC adipogenic differentiation.[119] Studies of SNHGs contained in sEVs have focused on their regulatory roles in endothelial cell functions. An experimental study demonstrated that SNHG2 was upregulated in a macrophage cell line (TPH-1) by oxo-LDL treatment, and sEV shed by SNHG2 knockdown THP-1 cells inhibited the apoptosis of endothelial cells.[93] Similarly, MSC-derived sEV containing SNHG7 repress HG-induced endothelial dysfunction in human retinal microvascular endothelial cells.[94] In addition, sEV derived from SNHG9-overexpressing adipocytes alleviated inflammation in endothelial cells.[95] Endothelial cell dysfunction is a major contributor to diabetic microvascular- or macrovascular-related complications, such as retinopathy, nephropathy and cardiomyopathy. Thus, targeting sEV-SNHGs could be a future research direction for diabetic complication therapy.

6 | CONCLUSIONS AND FUTURE DIRECTIONS

To date, the relationship between lncRNAs and diabetic pathologies has been investigated extensively. However, the functional roles of lncRNAs carried in sEV in diabetes are still being elucidated. sEV lncRNAs have been shown to regulate diabetes-related endothelial cell function, lipid metabolism, skin cell proliferation and bone fracture healing. In particular, lncRNAs containing sEV derived from MSCs and ADSCs are promising therapeutic agents for diabetic wound healing and fracture healing.[82] However, using sEV lncRNAs as therapeutic agents in the clinic is still challenging. sEV lncRNA profiles differ according to the disease state and cell conditions; thus, clarifying the origin of sEV is a mandatory step for further functional study. Most studies obtain sEV from the serum of patients, sEV from plasma are a heterogeneous population originating from different cell types and

from different sources, which makes it difficult to establish their exact physiological roles and functions. Although various single vesicle technologies have been developed to unravel the heterogeneity of EV,[120,121] the current vesicle isolation and enrichment techniques prefer to identify the particular EV subpopulations based on physical properties only or based on compositions and functions.[122] In addition, sEV obtained from a conditioned medium of cells did not always have consistent results in vivo. Additionally, there are still problems with off-target effects, as the reported sEV lncRNAs all have multiple targets. In addition, although some mechanisms have been revealed for lncRNA sorting into EV,[123] such as RBP binding, miRNA mediating and subcellular localization affecting, further investigation is needed to understand the exact lncRNA sorting mechanisms. Additionally, the lncRNAs secreted by cells to exert paracrine effects or simply for elimination need to be further investigated. Overall, the mechanisms of lncRNAs and sEV lncRNAs in diabetes need more in-depth research.

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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ORCID

Wenguang Chang https://orcid.org/0000-0002-4151-7212

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